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Sir David Jack CBE FRS FRSE in interview with Dr Max Blythe
and in conversation with Professor Patrick Humphrey
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Interview III

Sir David Jack in interview with Dr Max Blythe

MB David, when we were last together in this studio, we got your career with Allen and Hanburys as far as 1972, and that was a great central point for a whole range of happenings. You'd had the life saving find of salbutamol and that had raised enough profits to actually build you a new department. We got that department in place in 1972 and a whole range of things proceed from that development. Last time we were talking about asthma and obviously salbutamol and the two-pronged attack on asthma with the steroids coming in. Was it 1968 that the steroid treatment to go with salbutamol came in?

DJ Yes, 1972 was the introduction of beclomethasone dipropionate.

MB Right. So, 1972 was actually when it came in. So, 1972 was this colossal year. Perhaps we could follow today the number of themes that emanated from 1972, but I'd start by saying that the whole thing seemed to rest a lot on the new strategy that you'd found at looking for drugs: looking at protein receptors and selectively having a look at their properties and their binding potential, and then looking at analogues?

DJ Yes. Well, that in essence is true. It was as a result of rationalising to myself how it could be that adrenaline affected every adrenoceptor in the body, and salbutamol, with only two structural changes in the molecule, should not have any alpha effects at all and should have only some of the beta effects. In rationalising that, it came to me very simply as to one of two things. First, receptor proteins are more varied than had been commonly supposed until then, and they are findable by exposing them in suitable tissues or preparations to analogues of the natural transmitter. These analogues, the unnatural ones, will interact with the receptor proteins, which are really catalysts. The only difference between them and enzymes is that enzymes, they can form covalent bonds and receptor proteins of the kind of adrenaline… or beta receptors anyway, we are really dealing with… they introduce conformational changes and activating changes in the receptor protein. The thing I knew then was that when you expose a receptor protein, let's say the $beta_2$ receptor, to an agonist, the complex is formed. Now, the nature of that is unique for every agonist because they are chemically different. Secondly, these complexes vary in two things. Firstly, in catalytic ability, for catalysing the next event down the scale, which is the processing of G-proteins on the inner side of the cell membrane. So, high catalytic activity equals high efficacy in pharmacological terms – that's all that efficacy is. It's a measure of the catalytic ability or capability of the agonist receptor protein complex. And that is the first determinant of the activity of an agonist: high catalytic activity equals high activity. The second characteristic is that these vary not only in catalytic

ability, but they vary in stability, and the most efficient way of making use of efficacy is to produce a more stable complex. Because really for the duration of a receptor occupancy, as you increase it, instead of going on, off, on, off, you have continuing agonism and that is much more efficient than intermittent. So, I knew then that the two determinants were first, stability and secondly, catalytic ability, and of course you can measure these things. Firstly, by simply measuring potency. Stickability or stability with an agonist like this, you can measure by using superfused preparations, for example, a piece of guinea pig tracheal muscle. Superfuse and apply a stimulus, which is going to make it contract, maintain the stimulus and superfuse with adrenaline to get a very quick onset of action, and then replace the adrenaline-containing Ringer's solution with drug-free, and then you get rapid on and rapid off. You know then that the drug goes on and off the receptor quickly and that it's highly potent and highly catalytic. If indeed you produce a reasonably stable complex what happens is you have perhaps a bit of a slower onset, but it's the offset that gives you the answer. You see, instead of recovering quickly within a minute or so, if, in fact, you have a slow offset, the most usual explanation of that is that the drug receptor complex is more stable. And, of course, the same applies to blockers, in which case you are not dealing with efficacy but it is the stability of the complex you form which is the only determinant of potency, and if it is stable enough, it determines the duration of action. An insurmountable blocker simply forms stable complexes with the receptor protein. These are the rules of the game, so you change your structures in order to get the necessary affinity. Now, the necessary affinity can only come with receptor proteins by having non-polar interactions where you have alkyl chain or other non-polar groupings interacting with non-polar parts of the receptor protein. When that happens you are displacing, in the receptor protein, a non-polar water interface with a non-polar/non-polar interface with the exclusion of water. So, as you exclude the water you increase entropy and you reduce the free energy in the other one, that is the only general way, apart from covalent bond formation, which is bad news for the drugs. The only way you get the energy necessary is to have non-polar interaction of sufficient order to induce a stable conformational change. In the case of a blocker, of course, that is an inactivating change, and in the case of an agonist it's an activating change. And you find out, simply by altering the molecule, adding bits here or there...

MB Playing the analogue game.

DJ Right, and so if you put in this big non-polar grouping and you get non-polar groupings you get away with… if you make them too big, the receptor molecule won't receive them and activity goes down. In which case, it means that out, close to the binding site of the original molecule, there is this bit which is non-polar and beyond that, since it won't receive any more non-polar thing, you've almost certainly struck a polar patch. So, what you have to do then is put on the end of this non-polar bit a polar one to act as a bridge from there, hopefully, to the next non-polar bit, and that is how you can increase affinity. That is really much of what medicinal chemistry is about.

MB As you said, these were the rules of the game.

DJ Right.

MB And it stopped you scratching around; you've talked about chickens!

DJ Well, at least I had a systematic way of thinking which was dead simple and which I found personally satisfying, but in fact it was translating the Stephenson paper of 1956 called 'A Modification of Receptor Theory'[1] from pharmacological into ordinary chemical terms, and that had been a useful guiding light to me. So far it has worked and I'm sufficiently ancient now that I'm unlikely to change!

MB David, that was the background of the things we are going to look at. Also, a bit of that background had to be the way in which you'd taken the staff along from that rather difficult early period when everything had to be turned over and a new start had to be made. You've got one or two lieutenants and captains in hand now. I think you've mentioned a person there, an asthmatic, called Poynter...

DJ Desmond Poynter, yes.

MB ...and you've mentioned one or two people who were there. I think Poynter was rather an effective member of your team. Perhaps we could put the leaders of your team in place in 1972.

DJ Desmond Poynter was, by then, head of pathology. He was a parasitologist when I arrived at Ware and I really deported the parasitologist by stopping anti-infective work at Allen and Hanbury's when they were transferred to Glaxo. But Desmond, who was the head of parasitology, I recognised as a very sensitive biologist, so I said to him, 'Well, you have a choice. You can go with your parasitology to Glaxo, or you can stay here and set up a pathology department. Think about it for a week or two and then come back.' He assures me I talked to him this way on Friday and on Monday morning, 'Well, what are you going to do, Desmond?' Anyway, he stayed and he's a very close friend of mine. He is not the quickest pathologist I have ever came across, but utterly honest and dependable and very sensitive. So, that was Desmond and he was at Allen and Hanbury's when I arrived. Roy Brittain was also there. Now, Roy ultimately became research director on the site, but then he was an assistant in pharmacology. The head of pharmacology left, a man called Patrick Darcy, because he reckoned he should have had the job I got because I had no background in research at all, and in that respect he was right.

MB So, that was uncomfortable for him?

DJ Well, exactly. In all honesty, Patrick was probably right, but in any event he left. Then I looked around and asked myself, 'Whom do I know who is a good pharmacologist who would come and work given these primitive circumstances?' And I couldn't see anybody. Then I saw Roy Brittain, a tremendous enthusiast and at that time about thirty or thirty-one I suppose. A tremendous enthusiast, and bluntly I would say at that time and even now probably not the greatest of theoretical pharmacologists, but a natural leader of men. A great enthusiast, irrepressible and really a person that people will follow, with a very open mind for ideas coming from whoever, so he was not threatening anybody but was encouraging them. On the other hand he would not put up with any old nonsense. The people had to work and to

[1] Stephenson, R.P., 1956. A modification of receptor theory. *Br. J. Pharmac. Chemother*., **11**, 379-393.

work hard as he did. So, Roy played a key role as the prime organiser and motivator of scientists on the site, I think. Les Martin came to us from Bengers, which were bought ultimately by Fisons, I think, a biochemist of very wide experience. We didn't have bad chemistry before he came, but when he left we had a high quality biochemistry department.

MB He put all that in place.

DJ Absolutely. A first-class man. Even to the day he retired, he had this interest in detailed science, which certainly I lost a long, long time ago. When we got the mass spectrometer, for example, to do the biochemical work he was the expert at it within a month or two, together with others. But he was a tremendous help. As far as chemistry was concerned, when I first went there, I asked two friends of mine to come and join me, one was Alec Ritchie and the other was Norman Harper. Now, Norman had been a senior lecturer in Chelsea College in medicinal chemistry and we had worked together as lecturers in Glasgow, and Norman came. Alec Ritchie was also from Glasgow, a PhD chemist, with an encyclopaedic knowledge of chemistry and he was in charge of chemical development. Now, Norman left after a couple of years to become head of the School of Pharmacy in Birmingham and Alec took over, but these two changed the chemistry in Allen and Hanburys. We became proficient rather than almost amateurish. Don't show this to people who were at Allen and Hanburys during that period, but we were a bit amateur! So, these were the key appointments from outside. We didn't bring in a pharmacologist from outside, Roy Brittain did that, and one of the reasons he got the job was that as a young man he had an appalling smash on a motorcycle and he was left with a stiff leg and was deaf in one ear. He used to use it as Nelson used his blind eye. I am sure he could hear when he wanted to. But, in any event, I looked at Roy and this man was irrepressible after this appalling accident and I said, 'Well, I don't know about your pharmacology, Roy, but there's nothing wrong with your character.'

MB A sparkling human?

DJ Oh yes, a most unusual man. In fact, you can hear Roy in any environment because he's a noisy fellow with a cackle of a laugh. A sterling individual. But the reason, very simply, that I did not bring any pharmacologist from outside was, firstly, I couldn't think of anybody I'd want who would be likely to come, and, secondly, I intended to be the *de facto* head of pharmacology myself, which is a bit presumptuous maybe, but that's what I decided to do and that in essence is what happened. Wilfred Simpson was our medical director. In fact, he was the great grandson of Simpson of chloroform fame and he was the medical director when we developed salbutamol. A very bold experimenter. In fact, with all the new drugs when Wilfred was there, I took them first under his supervision before other volunteers got to them, and he took it then under mine. Because it was such a personal thing you could move very quickly.

MB You were saying last time how quickly you could really get to work?

DJ With a small show you can move very quickly provided you are willing to make the decisions, but if you don't make the decisions you'll take as long as you like. Better to make the decision even if it's wrong, at least you get it out of your

system. So, these were the people who transformed the pharmacology and research at Ware and the achievements through the years very simply were, firstly, to change radically the treatment of asthma by inhalation drugs, of which we have spoken already, and, secondly, to change the treatment of migraine, and we are going to talk about 5-HT in a little while and of the control of the side effects of chemotherapy of cancer. These drugs came from the 5-hydroxytryptamine [HT] programme. So, these are the two programmes which in my mind are the important ones and the most innovative, because in each case we were doing something different. Ranitidine on the other hand was a huge drug and Zantac ultimately...

MB You mentioned the starting point of that was about 1972. When we last talked, we just got the beginning of that story. But if we could go back one step further, labetalol, I think, was slightly earlier?

DJ Yes. Well, I'll talk about labetalol in a minute. But, ranitidine, this may be on the earlier tape, that for us was simply a piece of opportunistic research following James Black's demonstration of histamine as a physiological mediator. So, the credit for the innovation of H_2 block goes to Jim Black, and luckily for us we found a better drug.

MB I mean, once you'd heard Black you just came back and switched straight into your systematic approach looking at receptors?

DJ Absolutely.

MB And building analogues?

DJ In any case, it worked. You asked about labetalol. One of the things when you're trying to make beta-agonists in adrenaline analogues, if you fail to make an agonist, you make a blocker. So, we had any number of weak blockers of the actions of adrenaline on heart muscle - $beta_1$ blockers. Now, the prototype drug then was propranolol. It came from ICI again, from Jim Black, and it was on the market, first for controlling anginal pains and increasing exercise tolerance in patients with ischaemic heart disease and, ultimately, following the work of Brian Pritchard at University College, London, used as an anti-hypertensive agent. In fact, that is now the main use of beta-blockers, to control high blood pressure, but it's almost an irrational drug to use, although effective. It found a big place because it had relatively fewer side effects than the drugs that went before. It was not entirely rational, you see, because the thing with drugs like propranolol is that it reduces blood pressure because it reduces cardiac output. In fact, when you give a beta-blocker to a patient with high blood pressure, even though you have made the heart rate slow and reduced the cardiac output, the blood pressure doesn't immediately fall because the body, in response to the reduced cardiac output, constricts the peripheral vessels and the blood pressure is maintained. So, you have a reduced cardiac output and you still haven't reduced peripheral resistance, but given time the body finds that it cannot change the cardiac output and so it adapts and it accommodates the reduced cardiac output. You end up then with the blood pressure down because the cardiac output is down, but the peripheral resistance is still relatively high. So, you've diminished blood flow and that is why the principal side effect of these things is cold feet, cold hands and so forth, but nevertheless they are very effective drugs and they are cardiac sparing. We

were looking again for something different if we could and it came to us again by accident - one of the analogues in the salbutamol related series, instead of a saligenin we used a salacaymite structure. Now, the salacaymites were beta-blockers and with N-tetra butyl substituent were just ordinary beta-blockers. With phenoxyisopropyl, the thing that was surprising though was that we were doing a dog primary screen, giving an intravenous infusion, and in the ordinary way you don't get a fall in blood pressure in the dog with a beta-blocker, but with this one the blood pressure fell, so there was something different about this one. We found out later that that drug and the one derived from it, labetalol, in addition to blocking beta-receptors in the heart, it blocked alpha-receptors at the periphery. So, what happened when you gave that drug was that instead of the cardiac output going down, in fact, the cardiac output was scarcely affected, but the peripheral resistance was reduced. When you give an alpha-blocker on its own what happens is that the blood pressure goes down and that stimulates a reflex tachycardia, but with the beta-blocker there you don't have the tachycardia, you don't have the reduced or the increased cardiac output and so you produce a more normal circulation.

MB So, this was a considerable find?

DJ That was a considerable find. Unfortunately, the mechanism also contained an Achilles heel because, you see, the effective dose response curve for a simple beta-blocker is the one that relates fall in blood pressure to cardiac output. Fall of cardiac output, like so, fall of blood pressure. In fact, even if you give very, very big doses, you can only reduce the blood pressure so much and it doesn't go down any further, so you don't get excessive postural hypotension. Whereas with labetalol, the effective dose response curve is the one that relates peripheral resistance to blood pressure. Instead of forming an asymptotic curve, the peripheral resistance just keeps on going down. So, you have to titrate the dose to get the right level otherwise you do get postural hypotension. In fact, that was the problem with the drug, because doctors knew that with ordinary beta-blockers they could simply write down the prescription for whatever dose it was and it would work and there wouldn't be a lot of problems or side effects. With this one they had to get the right dose and that was enough to make it useless.

MB Did it take to the market?

DJ Yes, it really had a special place. It never was a big drug by the standards of the other ones, anyway. For us, it was a small drug at that time. But we may have missed a major trick there because there was recently from Smith Kline Beecham an alpha beta-blocker, whose name escapes me at the moment, which has now been found to be extremely beneficial in severe heart failure. I'm sure as I can be that this drug would be also because there you are protecting the heart, putting a governor on it, with a beta-block and also you are reducing afterload and reducing the peripheral resistance, so a failing heart is able to cope with this new situation. So, if you want a cheap alternative to the Smith Kline Beecham one, then I'm pretty sure that would be it. In any case, that's water under the bridge and we didn't think of it at the time.

MB A trick missed but probably something for the future even?

DJ This came to the market in about 1975, I suppose, and still has a special place though in hypertensive crisis and it is sometimes put in intravenously or by mouth, but it will bring the blood pressure down quickly. So, that was Trandate or labetalol. Do you want to know what other research projects we were up to in the Seventies?

MB Can we just put one point in at this stage? You mentioned research and we've mentioned animals in research a few times, Sir David. Perhaps at this point we should actually take a look at your view of animal research because it's obviously quite a difficult area and an area which one must form quite strong opinions about to work in that arena and use a lot of animal life?

DJ Okay. Well, there are two cardinal points in this, as far as I am concerned, and by the way I was the chairman of the Research Defence Society for a number of years, ten years maybe. Our job was to explain to people why it was necessary to use animals if we were going to make major advances in medical and surgical practice. The reason you have to use animals is very simple. One, before you give a new substance to any human being, you must have very good reason for supposing that you are going to do something useful for them and to do them some good. Now, the only evidence you can have for that is if you have tried it in animals. For example, with high blood pressure, you try it on an animal and does it lower the blood pressure; you try it on a hypertensive animal, does it lower the blood pressure and what are the side effects? You cannot measure blood pressure *in vitro*, right? Similarly, anything involving the central nervous system, you cannot test it in isolated terms and similarly when we come to the second point. So, this is evidence that you are likely to do good. The least I would expect of a new anti-hypertensive agent, for example, is that it will lower blood pressure and in an acceptable way it will produce a more normal circulation and not cause use-limiting side-effects, but you'd have to have evidence from animals that that would be so. The second thing is that you have got to be reasonably sure that you are not going to do disproportionate damage to the person who's taking this drug, and the extreme example of that, of course, would be in drugs which cause malformation of babies so that you get teratogens. You cannot identify a teratogen other than by using animals. You cannot do it *in vitro*. When you do a test of that kind you test all sorts of things, sexual behaviour in the animals and behavioural features generally. Do you get implantation? Does the foetus develop normally? Is it delivered normally and having been delivered, is the baby normal? Now, there is no way you can give a drug to a human being who is likely to be pregnant without having strong evidence that this does not damage the foetus in animals. So, anybody who tells you that you do these things either *in vitro* or by computers has not understood the problem, quite frankly. So, that's one side of the problem and that's the point of view of human beings, if you like. The other responsibility though is that I believe very strongly that no animal should be used in an experiment except to answer a question that is worth asking in the first place. The question is, 'Is this teratogenic?' It may be of value for migraine but is it safe to give it to pregnant women? If the question is worth asking, it's worth doing the experiment. But animals should never be used except for important ends. And secondly, the design of the experiment must be capable of answering the question. People go on about using the minimum number of animals, but that may not necessarily be the right thing to do. You've got to use the right number of animals that will give you a statistically valid figure otherwise you have to do it again. So, I

hope that outlines very briefly why the use of animals is essential and will continue to be in my view.

MB I was also going to ask you, David, at this particular stage, about the personal aspect of this work. We've obviously shown that you were, by now, leading a team that was getting somewhere. You were making profits that were sustaining all sorts of future development programmes and you were getting the satisfaction of seeing drugs come on to the market that were really making headway for Glaxo, the first real international products of Glaxo. For you, as a person who'd come up slowly and worked through development and had come to research quite late, what were the personal rewards when you saw a drug like salbutamol? Was there a thrust to find more or was there a great satisfaction? I just wonder what it was like to be sitting in your chair when that happened?

DJ One episode I can bring to mind was when the inhaled steroid came on, Becotide, inhaled beclomethasone dipropionate. David Harris brought to me a small boy with his mother and they'd shown me pictures before of this little boy, a severe asthmatic with a pigeon chest and all sorts, and then this little horror, this little monster, arrives in my office after steroid treatment and he was running around all over the place. Frankly, I found that very pleasing, that we were doing something useful, so one saw immediately the effect on this family. Another one of the same sort, although I didn't meet this girl personally, involved one of the men who did the earlier studies, a Scotsman called Harry Morrell-Brown who operated in Leeds, I think, it was at the Asthma Research Clinic, and Harry showed me a picture of a young girl before and after. Before, she was on systemic steroids with a blown-out face and all sorts of things and then she went on to inhaled steroids, successfully transferred, and there you saw the slim figure that was inside the other one. And Harry showed the slide showing this Cushingoid young girl and seeing her mother was very worried about her, and then he showed the next one and her mother was still very worried about her, the number of boyfriends she had around her, so you can't win them all! So, the benefit to patients I would think is the most satisfying thing. The second thing, of course, is to see your organisation get bigger, so you can do more things and a team of people who got on very well. One of the great merits of the team we had together was that they got on.

MB It was a remarkable team, wasn't it? They were bright and they got on?

DJ Well, Roy Brittain again tells me that early on, I don't know what they were arguing about, but they were in a vigorous dispute. This was early on in the time we got them together. And he said to me, 'What you told us literally was: "Now, listen to this. I do not want any more of this bloody nonsense!"' Off they went and sure enough, there was no more of that nonsense. So, you worked with friends.

MB Pinning our thoughts around that 1972 band, at that time that ship was going rather well. What I did want to come back to though was before I just leave the shadows of the Sixties, we talked about Sir Harry Jephcott being your first chairman, who tried to pull you in to a bigger research thing and you resisted and you kept clear of Jephcott's policies that were fairly constraining. He must have left somewhere in the mid-Sixties and you must have had a new boss?

DJ 1963, and we had Sir Alan Wilson who took over as chairman.

MB Did he come from Courtaulds?

DJ Yes, that's right.

MB Was that a success. Did that take you further ahead?

DJ Well, Sir Alan Wilson was a distinguished scientist, a physicist, and as far as I know he was the chap who was involved with the theory of metal and semi-conductors and suchlike, so he is a huge figure. Now, strangely enough, I never got to know Wilson. I found him a very remote individual.

MB I think you once said you took a step towards him and he...

DJ Took two back straightaway. He had around him a small coterie of people who might have been courtiers, I don't know. But all one would say of Wilson is this, he liberated Glaxo research and he provided the resource and let us do what we wanted to do.

MB He made it more international and took it into Europe. Is that right?

DJ He took the Glaxo organisation into Europe, but not into America or Japan.

MB Yes, not into America?

DJ He had good reason for that. In fact, when we had salbutamol, with other things promised - because by then we had got wind of Trandate off labetalol and inhaled steroids were coming on - I reckoned we ought to go into America because to get into America you must go in with a novel product. The other thing that never occurred to me is that you need an awful lot of money. Wilson didn't bother to explain it to me and I went there with my chief, Mr Maplethorpe, and he listened but he didn't say anything very much and I really was very disappointed. And instead of going into America, he went into Europe and that was obviously a safer bet because it needed less money. The second reason, I think, was that he had gone into America with Courtaulds and had got the fingers very badly burnt and he lost a lot of money. So, Wilson then was a brilliant man but a remote man. I recently talked with his biographer, who was one of his PhD students, who had got no further with Wilson than I did. A pretty remote fellow.

MB I've got a feeling that he linked you up with Sherring in the most terrible deal. Is that right?

DJ Yes, well instead of going into America with salbutamol, and labetalol, I may say, he licensed it to Sherring under absurdly generous conditions and so the result of that by the way was not that it was absurdly generous, but that Sherring made a mess of developing salbutamol in America and it didn't come on the American market until 1981. So, that held it back ten years at least.

MB And you were on this ridiculous percentage?

DJ Well, I was on no percentage but Glaxo was on seven and a half per cent, I think it was, exclusive with no time limit on the time it got to market, so it really was a laughable agreement.

MB How did Sherring explain that delay because you'd delivered something that was going on the home market without a problem?

DJ You are intruding on private grief now! Very simply, two things happened. First, they insisted on making their own pressurised inhalers and having gone three-quarters of the way through the definitive clinical trials, they found that they had done a stability test by measuring how much drug was in the can. And, sure enough, the right amount was in the can; what they had not noticed was that half of it was stuck to the side of the can and wasn't coming out. So, the whole of the first clinical research programme was invalidated because they had no notion of how much drug went in to the patient and they had to start again. Around that time it was also found that drugs of the salbutamol kind induced a bizarre kind of tumour in the rat, a smooth muscle tumour, totally benign, a mesovarian leiomyoma, and we had to show that this was a class effect which was relevant only to the rat and that took a long time because these leiomyoma took up to a couple of years to develop.

MB So, the whole American side of it got hung up on that?

DJ They got stuck on that, and the beta stimulants that were on the market stayed on and the ones that were not on were kept off until this problem was cleared up. And it was cleared up in our laboratories with an experiment I designed myself, because a drug that was on the market in America was terbutaline from Astra which was licensed to an American company, I forget which one, Ciba Geigy I think it was. But terbutaline was on the market and salbutamol was not. As far as I was concerned, they would be very similar drugs. Terbutaline had not been found to cause these tumours, mainly because the study had never been done for long enough. So, one set up an experiment, much to the annoyance of Astra I may say, comparing salbutamol and terbutaline at equivalent doses and doses big enough, hopefully, to give you continuous beta agonism. But half of the salbutamol group was also given a large dose of a beta-blocker, propranolol, and in the event we were dead lucky because it turned out that the salbutamol and terbutaline groups had the same number of leiomyoma and the ones with the beta-blocker had none. So, it was a pure agonergic reaction. And we also had every person with asthma taking beta-agonists that we could lay our hands on - the surgeons hand on - with a laparotomy, for whatever reason, and that was done in London and elsewhere. We came to the conclusion, therefore, that there was no sign of such an effect in human beings and, secondly, it was really a class effect of beta-agonists; it was not a tumorgenic effect in the ordinary sense of the word. So, that took ten years to sort out.

MB So, Sherring did you no great favours?

DJ Well, I must admit I was not too well disposed towards Sherring. I don't often go off, but certainly I was not very amused.

MB David, we've been talking about salbutamol, let's stay with that theme, let's stay with the asthma story, it's the kind of foundation. As you, at one stage, said to me, 'The new laboratories were effectively built on foundations of a Roman road at Ware.' These were the foundations of your whole future expansion of research, but you weren't happy with this two-pronged approach, the steroid and the salbutamol. You were still unhappy as we move into the Seventies; you were still looking for a better customer treatment. I want to go into that now.

DJ We had to improve, if we could, the treatment of asthma.

MB What was wrong with the existing one?

DJ Well, the first one was given by inhalation and many people don't enjoy taking inhaled drugs or prefer to take pills by mouth. For children and so forth, it's much easier to dose by mouth. So, what we had hoped to do was to find an orally active analogue of salbutamol which was an effective bronchodilator without causing the side effects that salbutamol caused, the tremor, the changes in blood pressure and so forth. We failed. In fact, we tried to do that for too long and I think we abandoned that effort in about 1977 or so, after much effort. So, that was one approach that failed. The other important drug that was invented in Britain at that time was cromoglycate, Intal from Fisons. Now, it's a different kind of drug altogether, which is alleged to be anti-inflammatory. But it does something useful in asthma, which you can show very easily, because if Intal is inhaled then exercise-induced bronchial constriction is abolished for a short time. So, Intal undoubtedly does something useful. So, we tried to find an Intal, except we were looking still for firstly an inhaled, but above all a systemically active Intal. I had three drugs in the clinic, all on the basis of exercise-induced bronchial constriction, and three times it looked interesting, including an orally active one, but when we went to double-blind control studies in patients, the activity virtually disappeared. I'm a slow learner and it took me a long time to realise that cromoglycate alone was not really a serious advance in the treatment of asthma, except maybe in young children. So, we abandoned that. You don't win them all. Also at that time, probably ahead of the game, I asked that we prepare some phosphodiesterase inhibitors to stabilise the cyclic AMP levels in any cell. It increases them in effect, and of course adrenaline at beta-receptors, the next messenger is cyclic AMP. It also happens that not only are the bronchial muscle cells under cyclic AMP inhibitor control, so are the mast cells and so are the eosinophils and so are the lymphocytes and so forth. Phosphodiesterase, I thought, would be a bronchodilator and in addition suppress the activity of other inflammatory cells. Now, as it happens we tried it and we found a drug which by inhalation was about as good as salbutamol. In fact, looking back on it, it was not well tolerated by dog and so forth, but even so we should have taken that further.

MB That was a missed opportunity?

DJ I believe so. Mind you, the reason we didn't take it any further at the time was because it was demanding major attention for development capability, and then we had started to develop ranitidine which turned into this £3 billion a year product, so there was no contest there, but I regret that I forgot that one. Again, the idea was sound because today a vast number of companies are looking seriously for selectively acting phosphodiesterase inhibitors.

MB So you were on the right track?

DJ Because there would not be a value in asthma only if they worked and were tolerated systemically. Joint disease and inflammatory conditions involving the usual collection of cells involved in inflammation are all under inhibitory control.

MB So you can see a future for that regime?

DJ I think if that can be done without causing undue side effects, then I think in five years or ten years time, watch that spot. So, that was another one that we tried and failed. Another one we tried and failed were prostaglandin E_2 analogues. Prostaglandin E_2 inhaled is a bronchodilator with an action very like that of isoprenaline. Quick on, quick off. But the other thing about it, of course, is that it is an irritant and causes coughing, so prostaglandin E_2 itself was no use. On the other hand, prostaglandin E_2 not only inhibits the contraction of smooth muscle but also inhibits these inflammatory cells, so there is a possibility there of an alternative to phosphodiesterase inhibition.

MB And they never got rid of the coughing?

DJ And in fact we had marvellous prostaglandin E_2 analogues which were long acting, but when inhaled by human beings they caused coughing which was very annoying.

MB That must have been terribly sad?

DJ Well, Patrick Humprey who we are going to talk to in a wee while, that was one of his projects, but it didn't work. So, we come then to 1981. Salbutamol is doing well, inhaled beclomethasone dipropionate is doing well...

MB It's even in America by now!

DJ Yes, the next stage that happened was that when we came to market in America, it was already a well-known drug. People were importing it from Canada across the border into America, so what could we do to make salbutamol interesting? We held a closed symposium in Boston in the Copley Plaza Hotel with distinguished experts from around the world and we published the proceedings and sent it round to every chest physician in the land, as far as I know, simply to make them pay attention. But I was asked by the chairman of the symposium to take part and to speak to a theme about whether it is possible to make better a bronchodilator than albuterol? Now, I knew we couldn't do it by mouth. Was it possible to make one by inhalation? And the answer came to me - yes. Now, two ways of doing it occurred to me. The first I disclosed at the meeting and the essence of the first one was this. You see, bases such as salbutamol or quaternary bases such as atropine methonitrate, they are cleared from the lungs and airways relatively slowly, it takes about three or four hours. That's why you get a long duration of action of three or four hours. Whereas cromoglycate, by inhalation, you find that the drug appears in the urine very, very quickly. So, the acidic drug is very rapidly mobilised and the basic drug is much more slowly mobilised. Why? I think possibly, in asthmatics there is any amount of

mucoprotein and mucoprotein have acidic groups in abundance, so I thought maybe acting as an ion exchange system. You have a base comes in, so you have an impeded diffusion because of ion exchange, like a chromatographic column, if you like. So, one said to them that it is possible that if we make something with higher affinity for mucoprotein and, provided it is sufficiently potent, it will diffuse, disengage and you will have a long duration of action. That is one possibility. That's the one I disclosed because I thought the problem impractical. The other one I thought of was much simpler. By the way, if you're interested in publication in disclosing that, it's there. It might even work! The other way of solving the problem that occurred to me was that I had concluded, as I was telling you earlier, that there were agonists that formed complexes with the receptor protein of varying stability with receptor proteins of the kind for adrenaline, at least at the beta-receptor protein, and prolonged receptor occupancy is consistent with continued activity. One said, 'Very well, what we have to do is to change salbutamol or change adrenaline into a molecule which engages the receptor protein and sticks. We must make it more sticky so that once it engages, it doesn't come off and then the duration of the action of such a drug would be determined by the lifetime of the occupied protein.' Out of that came salmeterol, by the principles we talked of earlier. Salmeterol is salbutamol but with a very long, flexible, essentially non-polar tip, but in that there's an ether oxygen and six carbons which is essential for activity, and that again is the bridge between lipophilic groups, two lipophilic groups with a polar bit in between. It needs a linking piece.

MB David, you first started thinking down that avenue in 1981 we've said. How long did it take to actually come up with salmeterol?

DJ Well, it came on the market in 1991, I think. Ten years.

MB But you knew you had it in the mid-eighties?

DJ Oh, early on. Well, one knew very soon. In fact, I can tell you that my colleagues, who knew better than I did, didn't want to do the project at all because the literature is full of accounts of desensitisation of beta-adrenal receptor proteins and this kind of drug I was describing would certainly desensitise the receptor protein. I didn't believe it for two very simple reasons. Firstly, if the body ever became easily sensitised to the action of adrenaline or for that matter steroids, it would be a design fault of catastrophic dimensions because these are the two major protective hormones, so I couldn't believe that would happen. The other thing is, you see, if you take a piece of guinea pig ileum or guinea pig tracheal muscle, superfuse it with isoprenaline or adrenaline, provided you don't smother the thing, in tolerated concentrations it goes on hour after hour after hour after hour, despite what's in the book. And yet my people still said, 'It's in the booklet, David, read it.' I had read it. So, I asked them to do some experiments and with one drug in particular, clenbuterol, which is a different substitution altogether but has high affinity. I picked it because it has high affinity for the receptor protein. I said, 'Check clenbuterol and I will make you a forecast, it'll have a slower onset of action, but a longer duration on the superfusion than salbutamol.' Sure enough they did it and that's the way it turned out. I was lucky. By the way, the reason for that I won't weary you with now, but the reason I gave them was not the right one, but that doesn't matter. In fact, the reason is even more interesting, but we don't have time to go into it.

MB David, at that stage, we've got that salmeterol story on the way, and I'm going to come back to that because it's a major area of sales, but we've had some difficulties so I want to come back because that's late-eighties/early-nineties. Before we go, I want to go back to the migraine, 5-hydroxytryptamine story which is the other theme we're taking in today. It was essentially Patrick Humphrey's initiative?

DJ Well, it started in 1972, which as I have already explained to you was a special year for Glaxo when we had new pharmacology laboratories in Ware at huge cost, a million pounds, and it was paid for largely by money earned by salbutamol. We therefore had a bigger budget, we had new laboratories and one of the most important things that happened in 1972 is that Patrick Humphrey joined us as a new PhD. So, Patrick was asked by Roy Brittain and me to consider migraine as an applied research project because I always felt that our job is to find better medicines for common ailments that are not well treated and migraine clearly satisfied these conditions. But how? What should we do? Patrick agreed to look at migraine as a problem and came back and recommended that we work on 5-hydroxytryptamine.